Abstracts

Gregory L. Moneta, MD, Abstracts Section Editor

Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes

Nissen SE, Wolski K. N Engl J Med 2007;356:2457-71.

Conclusion: Rosiglitazone is associated with an increase in myocardial infarction and risk of death from cardiovascular causes.

Summary: Rosiglitazone was introduced in 1999 as oral treatment for type 2 diabetes. It is widely used as monotherapy or in fixed-dose combinations with either metformin or glimepirid. Rosiglitazone acts to lower blood sugar by increasing insulin sensitivity of peripheral tissues. Individual studies of rosiglitazone have confirmed its effect on reduction of blood sugar and improvement in glycosylated hemoglobin levels. Studies, however, were not powered to assess cardiovascular morbidity and mortality. In this article the authors reported results of a meta-analysis that included published literature, the Food and Drug Administration Web site, and a clinical trials registry maintained by GalxoSmithKline, the manufacturer of rosiglitazone. The analysis included studies that had a duration of >24 weeks, used a randomized control group, and provided outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, only 42 met the inclusion criteria for the analysis. Focus was on tabulation of all occurrences of myocardial infarction and death from cardiovascular causes.

A fixed-effect model was used to combine the data. In the 42 trials, the mean age of subjects was 56 years and the mean glycosylated hemoglobin level was 8.2%. The odds ratio for myocardial infarction in the rosiglitazone group compared with the control groups was 1.43 (95% confidence interval [CI], 1.03 to 1.98; $P = .03$). The odds ratio for death from cardiovascular causes in patients taking rosiglitazone versus controls was 1.64 (95% CI, 0.98 to 2.74; $P = .06$).

Comment: The authors acknowledge in the discussion of the article that a few events either way may have influenced the results of this analysis. Nevertheless, there seems to be no particular benefit for rosiglitazone other than reducing laboratory measures of glycemic control. Rosiglitazone has no known favorable effect on microvascular disease or other complications of diabetes. Given the results of this study, there seems little rationale for continued use of rosiglitazone for treatment of type 2 diabetes.

Elastin stabilization for treatment of abdominal aortic aneurysms

Isenburg JC, Simionescu DT, Starcher BC, et al. Circulation 2007;115: 1729-37.

Conclusion: Administration of pentagalloyl glucose (PGG) in the periadventitial area of the aorta slows development of abdominal aortic aneurysm (AAA) in an animal model.

Summary: Among other things, AAA is characterized by disruption or fragmentation of elastin and decreased medial elastin content. Treatment for AAA is surgical, and no pharmacologic therapy currently exists. In this article, the authors sought to explore the role of PGG, a potential elastin-stabilizing agent, for treatment of AAA.

PGG is a polyphenolic tannin. Tannins bind to elastin and make them resistant to enzymatic degradation. The authors tested the ability of PGG to enhance elastin stability and interfere with AAA development in a well-established AAA model in rats that uses calcium chloride to mediate aortic injury and induce an AAA. In calcium chloride-induced aneurysms, the authors delivered PPG periadventitially at two separate time points during AAA development. They then measured aortic diameter, elastin integrity, and other pathologic markers in PGG-treated aortas compared with saline-treated control aortas.

The periadventitial delivery of noncytotoxic levels of PGG inhibited elastin degeneration and attenuated AAA expansion. PPG hindered AAA development in the model without apparent effects on inflammation, calcification, and MMP activity. Despite high levels of proteinases from inflammatory cells in the wall of the aorta, PGG appeared to preserve the integrity of elastic lamina.

Comment: Growth of AAAs appears to be associated with elastin degeneration secondary to proteinases derived from inflammatory cells infiltrating the aortic wall. By directly targeting what appears to be one of the primary biochemical mechanisms of AAA development, this article suggests a pharmacologic therapy for AAA. Refining delivery mechanisms and dosage intervals are obviously future areas of research in this field.

Impact of obesity in arteriovenous fistula outcomes in dialysis patients

Kats N, Hawxby AM, Barker J, et al. Kidney Int 2007;71:39-43.

Conclusion: Obese patients have worse fistula survival than nonobese patients because of a high secondary failure rate of the fistula.

Summary: There appears to be a less frequent use of fistulas vs grafts in obese vs nonobese patients requiring hemodialysis. The reasons for this discrepancy are unclear and may be because in obese patients there is a lower rate of fistula placement, a higher primary failure rate (a fistula that was never usable for dialysis) of fistulas, or higher secondary failure rates (a fistula that failed after being used successfully for dialysis).

In this study, the authors used an institutional prospective computerized vascular access database to identify patients receiving a first fistula or graft during a 2-year period. Access outcomes were compared between obese and nonobese patients. Obese patients were defined as those having a body mass index (BMI) ≥ 30 kg/m^2.

During the study period, a first fistula was placed in 183 patients and a first graft in 205. Fifty-four of the fistula patients were obese, and 129 were not obese. Patient age, frequency of diabetes, coronary artery disease, peripheral vascular disease, and obesity were not different between patients receiving a fistula and those receiving a graft. Obese and nonobese patients were equally likely to receive a fistula (47.4% vs 47.1%). Primary failure rate of fistulas was similar in both obese and nonobese patients (46% vs 41%, $P = .45$). If a fistula was useful for dialysis, secondary survival was worse in obese patients (hazard ratio, 2.74; 95% conference interval [CI], 1.48 to 7.90; $P = .004$). Secondary fistula survival in obese vs nonobese patients was 68% vs 92% at 1 year, 59% vs 78% at 2 years, and 47% vs 70% at 3 years. A multiple variable survival analysis model that included age, sex, race, diabetes, coronary artery disease, peripheral vascular disease, fistula location, surgeon and obesity, found that obesity was the only factor predicting secondary fistula failure (hazard ratio, 2.93; 95% CI, 1.44 to 5.93; $P = .004$).

Comment: The authors found that many of the potential explanations for fistula failure in the obese patient vs the nonobese patient did not hold up to statistical analysis. Specifically, there was no difference in venous diameters, prevalence of transposed vein fistulas, or the prevalence of needle infiltration in the obese vs nonobese patient. A previous study (Am J Kidney Diseases 2002; 39: 92-101) found no association between BMI and risk of primary fistula failure. In that study, >90% of the patients were white, whereas in the current study, the primary population was black. It may be that unknown confounding variables other than obesity are contributing to the higher secondary fistula failure rate in the obese patient.

Mutations in *FOXC2* are strongly associated with primary valve failure in veins of the lower limb

Mellor RH, Brice G, Stanton A.WB, et al. Circulation 2007;115:1912-20.

Conclusion: Mutations in the *FOXC2* gene are strongly associated with primary venous valve failure in both deep and superficial veins of the lower extremity.

Summary: *FOXC2* is situated on chromosome 16Q24.3 and encodes a regulatory transcription factor that is implicated in vascular and lymphatic development. It is expressed on both endothelial and smooth muscle cells of developing blood vessels and is also expressed on venous and lymphatic valve leaflets. Homozygous male mice for *FOXC2* die during development with nonfunctioning blood vessels. A heterozygous mutation of *FOXC2* in humans results in lymphedema distichiasis, an inherited form of lymphedema. Patients with lymphedema distichiasis often have varicose veins. This form of lymphedema is thought to be caused by lymphatic valve reflux, and because *FOXC2* is highly expressed on mouse embryo venous valves, the authors postulated *FOXC2* mutations may be linked to venous valve failure and venous reflux.

The authors identified 18 subjects with a *FOXC2* mutation, three of whom did not have lymphedema. All 18 subjects were studied with duplex ultrasound imaging of the lower extremities for evidence of venous reflux. Criteria for venous reflux included peak reflux velocity of >10 cm/s and duration of reflux >0.5 seconds after release of distal compression. In this study, pathologic reflux was only diagnosed if both of these criteria were present. The subjects with *FOXC2* mutations were compared with a reference group of 12 subjects with no *FOXC2* mutation. Ten of these reference subjects were family members of participants in the *FOXC2* group. Every individual with the *FOXC2* mutation showed reflux in the great saphenous vein, but only one of 12 of the reference subjects showed reflux in the great saphenous vein ($P < .0001$). Deep venous reflux was also recorded in 14 of the 18 subjects with the *FOXC2* mutation.

Comment: This is the first paper to identify a link between a specific genetic mutation and primary venous valve failure in superficial and deep veins. It appears that *FOXC2* expression is required for valve development and maintenance of valvular integrity in the venous system of the lower extremities in humans. The role of *FOXC2* mutations in determining primary venous valve failure in the population in general certainly seems worth investigating.